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RETINAL DISORDERS

Efficacy and safety of ranibizumab 0.5 mg in Chinese patients with visual impairment due to diabetic macular edema: results from the 12-month REFINE study

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Abstract

Purpose To demonstrate the efficacy and safety of ranibizumab 0.5 mg pro re nata (PRN) versus laser photocoagulation for the treatment of Chinese patients with visual impairment due to diabetic macular edema (DME).

Methods REFINE was a phase III, 12-month, double-masked, multicenter, laser-controlled study in patients (aged ≥ 18 years) with DME. Patients were randomized 4:1 to receive either ranibizumab 0.5 mg or laser dosing regimen. Efficacy was evaluated as mean average change in best-corrected visual acuity (BCVA) from Months 1 to 12 versus baseline (primary endpoint), anatomical outcomes, treatment exposure, and safety were also assessed.

Results Ranibizumab was statistically superior ($p < 0.001$) to laser treatment, with a mean average BCVA gain of 6.8 letters (ranibizumab) over 12 months versus 1.1 letters (laser). At Month 12, mean BCVA gain was 7.8 letters (ranibizumab) and 2.5 letters (laser) from baseline. Patients in the ranibizumab arm received a mean number of 7.9 intravitreal injections, whereas those in the laser arm received a mean of 2.1 treatments. There were no new safety signals.

Conclusion Ranibizumab 0.5 mg PRN demonstrated a statistically significant and clinically meaningful treatment effect versus laser and was well tolerated in Chinese patients with visual impairment due to DME over 12 months.

Keywords Anti-vascular endothelial growth factor · Diabetic macular edema · Pro re nata · Ranibizumab

Introduction

Diabetic retinopathy (DR) is a leading cause of visual impairment and blindness in the global population aged 20–74 years [1, 2] and is an increasing concern with the rising prevalence of diabetes [3]. Diabetic macular edema (DME) is a common manifestation of DR and a cause of serious central visual loss and impairment in diabetic patients if left untreated [4]. Timely intervention in patients with diabetes can help to prevent vision deterioration and lower the risk of blindness due to DME.

This is particularly relevant for China, as at least 50% of its population (aged ≥ 18 years) have been shown to have pre-diabetes based on a 2010 nationwide survey [5]. In another nationally representative cross-sectional survey conducted in 2013 in mainland China, it reported 35.7% of population aged ≥ 18 years with pre-diabetes [6]. For patients with a confirmed diagnosis of diabetes, two epidemiological studies in 2642 to 7577 patients conducted in China in 2010 and 2011 have reported a high prevalence of DR (9.4% to 43.1% of patients,

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respectively) and its associated risks including longer duration of diabetes, higher plasma concentration of glycated hemoglobin (HbA_{1c}), higher postprandial blood glucose concentrations, and higher systolic blood pressure [7–9]. In a cross-sectional study of 17,985 patients in Beijing, the prevalence of DR was reported to be 8.1% [10].

Macular edema is a vision threatening complication of DR. In the Beijing Eye Study, which included 4439 patients with diabetes mellitus aged > 40 years, the overall prevalence of macular edema was 5.2% [11]. An epidemiologic study in the Shanghai city region in China identified 829 patients > 15 years old with diabetes, of whom 36 (4.34%) had macular edema [12].

Laser photocoagulation is currently considered the standard of care for visual impairment due to DME in China, which stabilizes rather than improves vision in these patients [13]. Furthermore, 13% of laser-treated eyes remain unresponsive to treatment and are at risk of progressive vision loss [13]. Therefore, there is a need for a treatment that not only halts progressive vision loss but also has a quick effect on improving visual acuity (VA) in Chinese patients with DME.

Vascular endothelial growth factor (VEGF) levels are elevated in the vitreous of eyes with DR; therefore, anti-VEGFs are an alternative treatment for patients with DME [14, 15]. Ranibizumab 0.5 mg was the first anti-VEGF approved for the treatment of visual impairment due to DME in Europe (2011) based on the data from the RESOLVE [16] and RESTORE [17] studies. These studies enrolled predominantly Caucasian patients and demonstrated significant and continuous improvement in VA over 12 months compared with sham or laser in patients with visual impairment due to DME. Currently in China, ranibizumab 0.5 mg is only approved for the treatment of neovascular age-related macular degeneration [18].

Here, we present the 12-month findings of the REFINE study that was conducted to provide additional data on the efficacy and safety of ranibizumab 0.5 mg compared with laser photocoagulation in Chinese patients with visual impairment due to DME.

Methods

Study design

REFINE was a phase III, 12-month, multicenter (28 sites) laser-controlled study conducted in mainland Chinese patients with visual impairment due to DME from November 2014 to January 2017. To minimize potential bias, the study had a parallel, randomized, double-masked design. Written informed consent was obtained from each patient before randomization.

The study was conducted according to the ethical principles of the Declaration of Helsinki, and the study protocol was reviewed by the Ethics Committee for each center. The study is registered at clinicaltrials.gov with identifier NCT02259088.

Patient population

The study population consisted of Chinese male and female patients aged ≥ 18 years with either type I or type II diabetes mellitus (according to the American Diabetes Association or World Health Organization guidelines [19]) and $HbA_{1c} \leq$ 10.0% at screening. Patients were included in the study with visual impairment due to focal or diffuse DME in at least one eye with a best-corrected VA (BCVA) score between 78 and 39 letters (inclusively, approximately 20/32 to 20/160 Snellen equivalent) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts at four meters. If both eyes were eligible, the eye with the worse VA at screening or baseline visits was selected as the study eye, unless the eye with the better VA was deemed to be more appropriate for study by the investigator based on medical reasons.

Patients with any type of systemic disease including those who had received treatment for it or any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to an extent that it might influence the assessment of the clinical status of the patient to a significant degree or put the patient at special risk; uncontrolled systolic blood pressure of > 160 mmHg or diastolic blood pressure of > 100 mmHg; and laser (panretinal, focal, grid) photocoagulation within 3 months prior to baseline visit (study eye) were excluded from the study. Detailed inclusion and exclusion criteria are provided in the A1.

Randomization and treatment

Patients were randomized 4:1 into two treatment arms to receive either ranibizumab 0.5 mg (pro re nata [PRN] dosing regimen) or laser photocoagulation (as needed according to ETDRS guidelines) (Fig. 1). A randomization list was produced by the interactive response technology (IRT) provider by using a validated system that automated the random assignment of patient numbers to randomization numbers.

In the REFINE study, the treatment regimen was based on the EU Summary of Product Characteristics 2011 (three monthly injections followed by PRN as per VA stabilization criterion) [20].

Ranibizumab arm All patients received three initial monthly ranibizumab 0.5-mg injections (on Day 1, Month 1, and Month 2), and sham laser photocoagulation on Day 1, followed by monthly ranibizumab based on a PRN dosing regimen until stable VA was achieved.

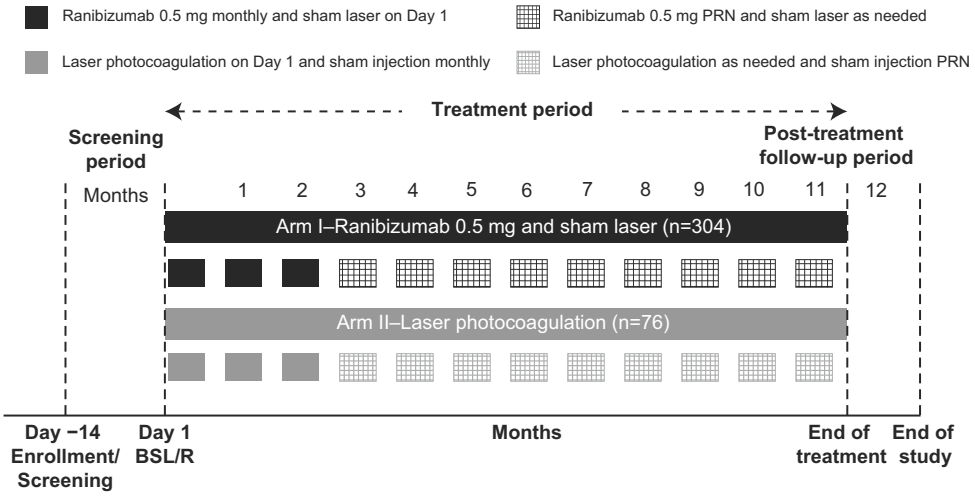

Fig. 1 Study design. BSL baseline, E enrollment, PRN pro re nata, R randomization

Stable VA was defined over three consecutive monthly assessments post-baseline, with study treatment given at each visit. If stable VA was achieved (at Month 3 or any later time point), treatment was stopped. Treatment with ranibizumab was resumed upon any loss of VA due to disease activity and continued until stable VA was reached again for three consecutive monthly assessments. Thus, after reinitiation of ranibizumab injections, a minimum of two successive monthly treatments were required.

Laser arm Patients received active laser photocoagulation on Day 1 (with option to split into two sessions with maximum of 4-week interval in between), and sham ranibizumab injection on Day 1, Month 1, and Month 2.

If stable VA was achieved, sham injections were discontinued. Monthly treatment with sham injections was resumed upon any loss of VA due to disease activity and continued until stable VA was reached again for three consecutive monthly assessments.

After Day 1, active laser photocoagulation was given as needed as per the ETDRS guidelines at intervals of no less than 3 months. Patients could receive a maximum of four laser photocoagulation throughout the study.

Rescue medication In case of lack of efficacy of the study treatment and when the investigator deemed it in the best interests of the patient to receive alternative treatment for DME in the study eye, the patient was asked to discontinue the study and was treated outside of the study protocol.

Treatment masking

In order to fulfill masking requirements, the site personnel consisted of a VA assessor, an evaluating investigator responsible for all other assessments and treatment decisions, and a treating investigator. Both the VA assessor and the evaluating investigator were masked to the treatment assignment, while treating investigator was unmasked and performed the treatment according to the assigned randomized treatment arm (A2).

Study objectives

The primary objective was to demonstrate superior efficacy of ranibizumab 0.5 mg monotherapy (PRN regimen driven by VA stability) compared with laser photocoagulation for the treatment of visual impairment due to DME in Chinese patients, as assessed by the mean average change in BCVA from Month 1 to Month 12 compared with baseline.

Secondary objectives were to evaluate the following: mean change in BCVA from baseline at Month 12; mean change in central subfield thickness (CSFT) from baseline at Month 12; proportion of patients with BCVA gain of ≥ 10 and ≥ 15 letters and loss of < 10 and < 15 letters from baseline at Month 12; proportion of patients with BCVA ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12; treatment exposure, number of retreatments, and retreatment patterns; and safety as assessed by ocular and non-ocular adverse events (AEs) and serious AEs (SAEs) over 12 months.

Other exploratory objectives were to evaluate the effect of treatment on DR as assessed by proportion of patients with changes on the ETDRS-diabetic retinopathy severity score (DRSS) on a 10-point scale (defined in A3), and proportion of patients progressing from non-proliferative DR (NPDR [ETDRS-DRSS on 10-point scale < 7 at baseline]) to proliferative DR (PDR [ETDRS-DRSS on 10-point scale ≥ 7]).

Efficacy and safety assessments

Study assessments were performed at screening (Visit 1), at baseline (Visit 2), and at monthly visits (every 30 days from baseline) until Month 12.

Efficacy assessments

Best-corrected visual acuity BCVA was assessed in both eyes at screening, baseline, Months 6 and 12, and in the study eye at all other visits. The measurements were performed in a sitting position using ETDRS-like VA testing charts at a testing distance of four meters.

Optical coherence tomography Optical coherence tomography was performed in both eyes at screening, Months 6 and 12, and in the study eye at all other visits to monitor disease activity, specifically CSFT. Images were also analyzed by a central reading center (CRC) which was masked to treatment.

Fluorescein angiography and color fundus photography FA was performed in conjunction with color fundus photography in both eyes at the screening, Month 6, and Month 12 visits to determine eligibility and monitor disease activity. In addition, the images were analyzed by a CRC to assess the presence and the type of DME, the area of leakage, and severity of DR by using the ETDRS severity scale for the study eye.

Treatment exposure and compliance

Patients were assigned to one of the two treatment arms by means of the IRT system.

Any deviations from the protocol or the administration of the active/sham ranibizumab injections as well as active/sham laser treatments were described on the dosage and administration record of the electronic Case Report Form.

Safety assessments

Safety was assessed by monitoring and recording all AEs and SAEs, conducting slit lamp and fundus examinations before dosing in both eyes at all visits and tonometry to assess intraocular pressure (IOP). IOP measurements (pre-injection and post-injection) were presented descriptively (absolute values and change from baseline) by monthly visit for the study eye, and in the subset of patients with IOP ≥ 30 mmHg.

Statistical analysis

A sample size of 380 patients was required (ranibizumab 304 and laser 76) to ensure that at least 300 patients received ranibizumab. Under this sample size, a statistical power of nearly 100% was expected with a significance level of 0.025.

For the primary analysis, the following one-sided hypothesis was tested at a one-sided alpha level of 0.025. The statistical hypothesis testing was based on a Cochran-Mantel-Haenszel (CMH) row mean score statistics using a stratified CMH test with original BCVA values as scores and with stratification according to DME type (focal, diffuse, honeycomb, and petaloid) and baseline BCVA score (≤ 60 letters versus > 60 letters). A three-way analysis of variance (ANOVA) model with treatment, baseline BCVA category, and DME type as factors were applied to generate least square (LS) means and two-sided 95% confidence intervals (CIs).

The primary analysis was performed on the full analysis set (FAS) with missing values imputed by the mean value last observation carried forward (MV-LOCF) method. The FAS comprised all patients in the randomized set (which consisted of all randomized patients) to whom the study treatment had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment to which they were assigned at randomization.

Missing values of other efficacy variables were imputed by standard LOCF method. For proportion of patients with a ≥ two-step in ETDRS-DRSS, an additional analysis was also performed on subgroup of patients with moderately severe NPDR or worse (ETDRS-DRSS on 10-point scale ≥ 5) at baseline.

Patient disposition was summarized by treatment by using the randomized set. Descriptive statistics were provided for patient demographics, baseline diabetes, and ocular characteristics for all randomized patients by treatment arm.

Descriptive statistics were provided for exposure to the study treatment by using the safety set. The safety set consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received. The statement that a patient had no AEs also constituted a safety assessment. The numbers of ranibizumab, laser, and sham treatments in the study eye were presented by treatment arm in frequency tables by visit and cumulatively over 12 months. Patients who received both active ranibizumab and active laser were analyzed under the ranibizumab arm in the safety analysis.

Results

Patient disposition, baseline demographics, disease, and ocular characteristics

A total of 384 patients were randomized; 307 to the ranibizumab 0.5 mg arm and 77 to the laser arm. The majority ($n = 342$; 89.1%) of patients completed the 12-month study period (90.9% in the ranibizumab arm; 81.8% in the laser arm; Fig. 2). The two most frequent reasons for premature study discontinuation in the ranibizumab and laser arms were patients'/guardians' decision to withdraw consent (2.6% and 10.4%, respectively) and AEs (2.0% and 5.2%, respectively; Fig. 2). Overall, 10.2% of patients ($n = 39$) had at least one protocol deviation (ranibizumab 10.4% and laser 9.1%). The

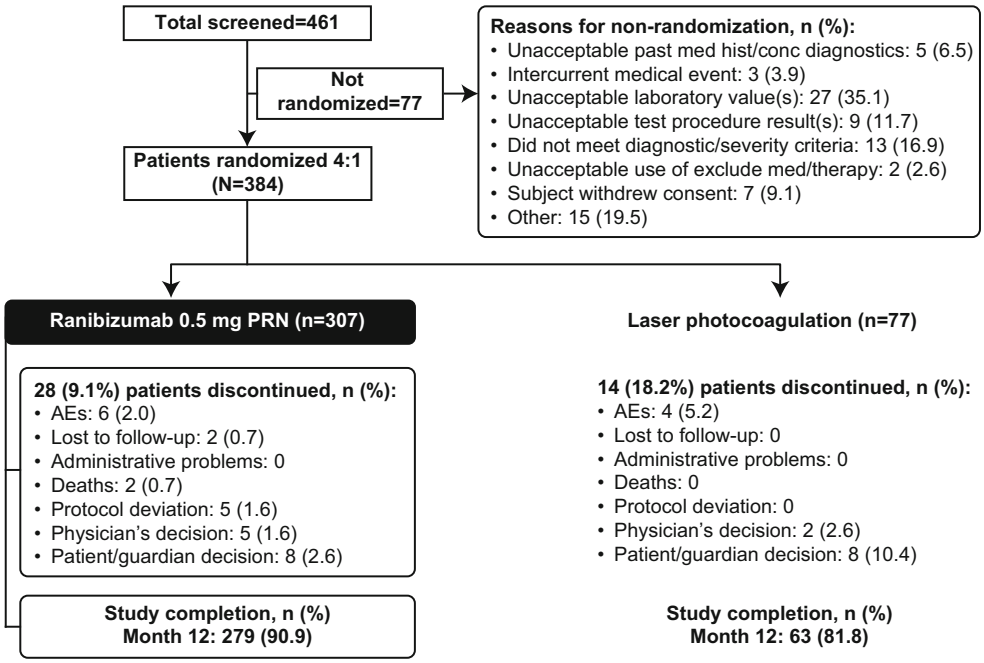

Fig. 2 Patient disposition (randomized set). The randomized set included all randomized patients to whom a randomization number was assigned. Percentages were based on the total number of patients in the randomized set in a specific treatment arm. AE adverse event, PRN pro re nata

most common protocol deviations with an impact on analysis were related to the eligibility criteria (3.6%) such as a change in diabetes medication within 3 months prior to enrollment (1.6%).

Patient baseline demographic, disease, and ocular characteristics were comparable between the treatment arms (Table 1). All patients were Chinese with a mean (± standard deviation [SD]) age of 58.7 (8.79) years; 53.6% were female. The majority of patients (99.0%) had type II diabetes and mean (SD) HbA_{1c} of 7.41 (1.14)%. Focal DME was the most frequent type of DME present at baseline (34.9%). The baseline mean (SD) VA was 59.3 (10.32) letters, and 96.9% of patients had an IOP of ≤ 21 mmHg; mean CSFT (SD) was similar in both treatment arms (ranibizumab 473.4 [166.13] μm; laser 475.0 [161.52] μm), and more patients had visible cysts in the ranibizumab arm (99%) (Table 1).

At baseline, a total of 290 (75.5%) patients had moderate non-proliferative DR or better (NPDR, DRSS < 4), while 94 (24.5%) patients had moderately/severe NPDR or worse (DRSS scores > 5) based on CRC assessment. DR severity was balanced between treatment groups.

Prior to the study, 58.3% of patients in the ranibizumab arm and 67.5% in the laser arm received laser treatment in the study eye, mostly for DR (62.3% of all patients with prior laser therapy) and DME (36.8%).

Efficacy and anatomical outcomes

Best-corrected visual acuity The mean (SD) average change in BCVA from Month 1 to Month 12 compared with baseline was 6.8 (6.58) letters in the ranibizumab arm and 1.1 (7.73) letters in the laser arm. The difference in LS means between the two treatment arms was 5.8 letters (95% CI 4.1, 7.5) and statistically significant ($p < 0.001$).

The mean change in BCVA from baseline at Month 12 was 7.8 (8.72) letters in the ranibizumab arm and 2.5 (8.78) letters in the laser arm (Fig. 3). The difference in LS means between the two arms was 5.4 letters (95% CI 3.2, 7.6).

A larger proportion of patients in the ranibizumab arm gained ≥ 10 and ≥ 15 BCVA letters at Month 12 compared to the laser arm (A4). Similarly, the proportion of patients with a loss of < 10 and < 15 letters was numerically higher in the ranibizumab arm compared with the laser arm (A4). The proportion of patients with a BCVA of ≥ 73 letters at Month 12 was numerically greater in the ranibizumab arm compared to the laser arm (36% versus 21.3%; A4).

A total of 35.8% of patients in the ranibizumab arm and 22.4% of patients in the laser arm reported an improvement by one or more steps in the ETDRS-DRSS 10-point scale from baseline to Month 12. At Month 12, 13.0% and 10.4% of patients had an improvement of a ≥ two-step change in the ETDRS-DRSS 10-point scale from baseline in the ranibizumab and laser arms, respectively. Out of the 69 patients in the ranibizumab arm with moderately severe NPDR or worse (DRSS ≥ 5) at baseline as determined by the CRC, 37 (53.6%) experienced a ≥ two-step improvement in the ETDRS-DRSS 10-point scale from baseline, compared to 7 (36.8%) of patients in the laser arm.

The proportion of patients who progressed from NPDR to PDR from baseline was 2.4% and 3.0% in the ranibizumab and laser arms, respectively.

Table 1 Baseline demographic, disease, and ocular characteristics (randomized set)

Characteristics	Ranibizumab 0.5 mg PRN ($n = 307$)	Laser ($n = 77$)
Age, years, mean (SD)	58.6 (8.70)	59.0 (9.19)
Age category (years), *n* (%)		
< 55	80 (26.1)	24 (31.2)
55 to < 65	151 (49.2)	30 (39.0)
65 to < 75	69 (22.5)	21 (27.3)
≤ 75	7 (2.3)	2 (2.6)
Gender, female, *n* (%)	168 (54.7)	38 (49.4)
Race, Chinese, *n* (%)	307 (100)	77 (100)
VA (ETDRS letters), mean (SD)	59.6 (10.53)	58.2 (9.43)
CSFT (μm), mean (SD)	473.4 (166.13)	475.0 (161.52)
IOP (mmHg), mean (SD)	15.4 (3.22)	15.0 (3.46)
Diabetes type, *n* (%)		
Type I	3 (1.0)	1 (1.3)
Type II[a]	304 (99.0)	76 (98.7)
HbA_{1c}, mean (SD)	7.44 (1.16)	7.30 (1.05)
Time since first diagnosis (years), mean (SD)	1.31 (2.01)	1.10 (1.47)
Time since first diagnosis (years), n (%)		
≤ 0.25	103 (33.6)	29 (37.7)
> 0.25–< 1.0	83 (27.0)	21 (27.3)
≥ 1.0	121 (39.4)	27 (35.1)
DME type, *n* (%)		
Focal	111 (36.2)	23 (29.9)
Diffuse	36 (11.7)	6 (7.8)
Honeycomb	67 (21.8)	22 (28.6)
Petaloid	93 (30.3)	26 (33.8)
Any visible cysts, *n* (%)		
No	3 (1.0)	1 (1.3)
Yes	304 (99.0)	75 (97.4)
Cannot grade	0	1 (1.3)
ETDRS DR severity score on original scale, *n* (%)		
10–12	0	0
14–53	268 (87.3)	63 (81.8)
60–85	36 (11.7)	12 (15.6)
98, 99, 0 or missing	3 (1.0)	2 (2.6)
ETDRS DR severity subgroup, *n* (%)		
Moderate NPDR or better (10 to 43)	231 (75.2)	54 (70.1)
Moderately severe NPDR or worse (47 to 85)	73 (23.8)	21 (27.3)
Missing	3 (1.0)	2 (2.6)

The randomized set included all randomized patients to whom a randomization number was assigned. Percentages were based on the total number of patients in the randomized set in the specific treatment arm. CSFT represents all data irrespective of types of OCT machines. DME types were assessed by Central Reading Center

CSFT central subfield thickness, *DME* diabetic macular edema, *DR* diabetic retinopathy, *ETDRS* Early Treatment Diabetic Retinopathy Study, HbA_{1c} glycated hemoglobin, *IOP* intraocular pressure, *NPDR* non-proliferative diabetic retinopathy, *OCT* optical coherence tomography, *PRN* pro re nata, *SD* standard deviation, *VA* visual acuity

[a] Patients with latent autoimmune diabetes in adults are classified as having diabetes mellitus type II

Anatomical outcomes A rapid and clinically relevant decrease in CSFT was observed from baseline during the first 3 months and was maintained up to Month 12 in the ranibizumab arm. At Month 12, the mean (SD) change in CSFT was higher in the ranibizumab arm than in the laser arm (− 146.5 [157.61] μm versus − 85.9 [166.60] μm). The

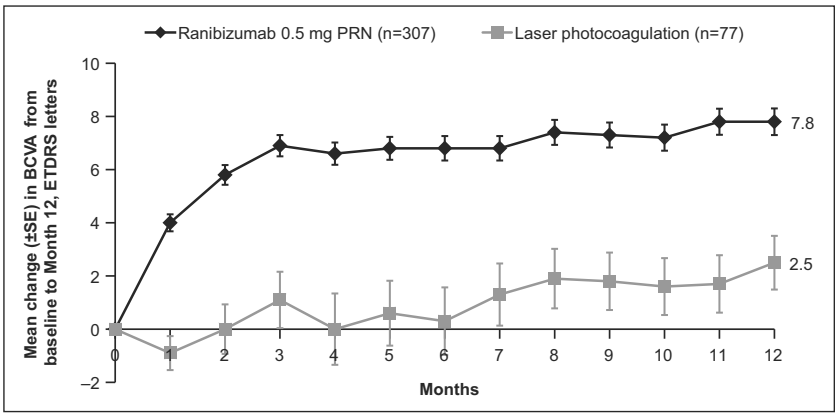

Fig. 3 Mean change in BCVA from baseline to Month 12 (full analysis set; LOCF). The full analysis set included all patients to whom treatment regimen was assigned. BCVA best-corrected visual acuity, ETDRS Early Treatment Diabetic Retinopathy Study, LOCF last observation carried forward, SE standard error, PRN pro re nata

difference in LS mean change between the two arms (ranibizumab 0.5-mg minus laser) was 72.5 μm (95% CI − 111.6, − 33.5 μm) and statistically significant ($p < 0.001$) (Fig. 4).

Treatment exposure The mean (SD) number of active study treatments received in the study eye was 7.9 (2.82) in the ranibizumab arm and 2.1(1.08) in the laser arm (Table 2).

The mean (SD) number of ranibizumab re-treatments, i.e., treatments administered from Month 3 to Month 12 after the first treatment interruption due to VA stabilization, was 1.6 (0.64) as shown in Table 3 with 32.6% of patients not requiring any further injections. The mean (SD) treatment-free interval for the ranibizumab arm was 3.0 (2.50) months, with a mean (SD) maximum treatment-free interval of 3.2 (2.52) months (Table 3). The proportion of patients in the ranibizumab arm with a maximum treatment-free interval of ≥ 3 months was 39.0%.

Safety outcomes

Overall, 25.4% and 57.3% of patients reported ocular AEs and non-ocular AEs in the study eye, respectively.

Ocular AEs In total, 27.4% of patients in the ranibizumab arm and 17.3% of patients in the laser arm reported ocular AEs of the study eye. The most frequently reported ocular AEs was IOP increased (ranibizumab 5.2%), followed by vitreous hemorrhage (ranibizumab 1.6%; laser 5.3%), conjunctival hemorrhage (ranibizumab 3.6%; laser 1.3%), and dry eye (ranibizumab 3.6%; laser 1.3%) as shown in Table 4. No cases of endophthalmitis were reported.

The most commonly reported ocular AEs in the study eye that were suspected to be related to the study drug and/or injection procedure in the ranibizumab arm were conjunctival hemorrhage (3.6%) and IOP increased (3.3%) (A5).

Non-ocular AEs Similarly, 57.0% of patients in the ranibizumab arm and 58.7% of patients in the laser arm experienced non-ocular AEs. The most frequently reported non-ocular AEs were hypertension (ranibizumab 6.2%; laser 13.3%) and nasopharyngitis (ranibizumab 6.5%; laser 9.3%) followed by upper respiratory tract infection (ranibizumab 8.5%; laser 2.7%) and cough (ranibizumab 5.9%; laser 2.7%; Table 4). None of the non-ocular AEs were suspected to be related to the study drug.

Overall, a similar proportion of patients experienced SAEs in both treatment arms (ranibizumab 18.9% and laser 21.3%).

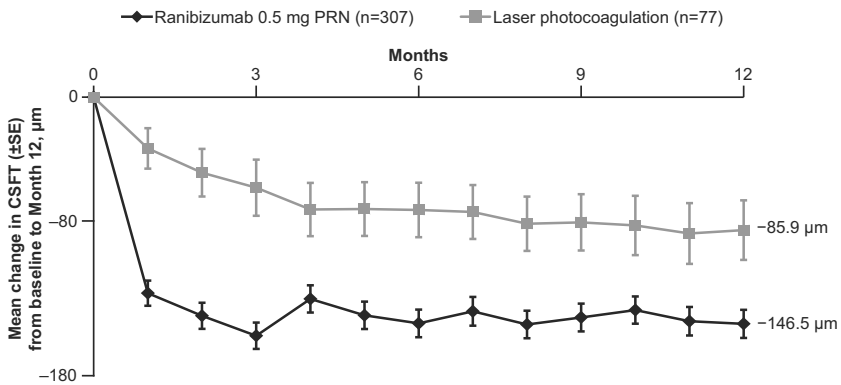

Fig. 4 Mean change in CSFT from baseline to Month 12 (full analysis set; LOCF). The full analysis set included all patients to whom treatment regimen was assigned. CSFT central subfield thickness, LOCF last observation carried forward, PRN pro re nata, SE standard error

Table 2 Treatment exposure and frequency of treatments (safety set)

Number of treatment	Ranibizumab 0.5 mg PRN ($n = 307$)	Laser ($n = 75$)
Total	2426	156
Mean (SD)	7.9 (2.82)	2.1 (1.08)
Median	8.0	2.0
Frequency of study treatments, *n* (%)		
1	5 (1.6)	29 (38.7)
2	2 (0.7)	22 (29.3)
3	23 (7.5)	13 (17.3)
4	14 (4.6)	11 (14.7)
5	23 (7.5)	0
6	26 (8.5)	0
7	34 (11.1)	0
8	33 (10.7)	0
9	44 (14.3)	0
10	40 (13.0)	0
11	33 (10.7)	0
12	30 (9.8)	0

The safety set consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Percentages are based on the number of patients in the safety set in the specific treatment arm

PRN pro re nata, *SD* standard deviation

Ocular SAEs Cataract was reported in 0.3% of patients in the ranibizumab arm and vitreous hemorrhage in 1.3% of patients in the laser arm (Table 5).

Non-ocular SAEs The non-ocular SAEs were reported in 16.3% of patients in the ranibizumab arm and 14.7% of patients in the laser arm. Two deaths were reported in the ranibizumab arm (one with sudden death and one due to pneumonia) which were considered not related to the study treatment and/or injection procedure (Table 5).

Discussion

REFINE is the first study conducted in the mainland Chinese population to assess the efficacy and safety data on ranibizumab 0.5 mg compared with laser photocoagulation, the current standard of care, in patients with visual impairment due to DME. In this study, ranibizumab 0.5 mg dosed PRN (driven by VA stability) demonstrated superior efficacy over laser photocoagulation in improving BCVA from baseline to Month 1 to Month 12 compared with baseline. The difference

Table 3 Number of ranibizumab re-treatments received from Month 3 (safety set)

Exposure	Ranibizumab 0.5 mg PRN ($n = 307$)
Re-treatment with ranibizumab from Month 3	
Total	319
Mean (SD)	1.6 (0.64)
Treatment free interval (months) for the ranibizumab arm	
Total	254
Mean (SD)	3.0 (2.50)
Duration of treatment free interval for ranibizumab from Month 3[a]	
Maximum treatment free interval (months), mean (SD)	3.2 (2.52)

A ranibizumab re-treatment is defined as an administration of ranibizumab injection at a scheduled visit following at least one non-missed visit where ranibizumab was not administered in the study eye due to visual acuity stabilization. Only applicable for patients in ranibizumab arm

[a] Missing visits were included in the calculation of the duration of ranibizumab treatment free intervals. The end of study visit was not included in any calculation. First visit of a ranibizumab treatment free interval had to be an attended visit, following a ranibizumab injection visit

PRN pro re nata, *SD* standard deviation

Table 4 Ocular (study eye) and non-ocular adverse events regardless of study drug relationship (≥ 3% in any arm) by preferred term (safety set)

Preferred term, *n* (%)	Ranibizumab 0.5 mg PRN (*n* = 307)	Laser (*n* = 75)
Ocular AE (total)	84 (27.4)	13 (17.3)
IOP increased	16 (5.2)	0
Conjunctival hemorrhage	11 (3.6)	1 (1.3)
Dry eye	11 (3.6)	1 (1.3)
Vitreous hemorrhage	5 (1.6)	4 (5.3)
Non-ocular AEs (total)	175 (57.0)	44 (58.7)
Upper respiratory tract infection	26 (8.5)	2 (2.7)
Nasopharyngitis	20 (6.5)	7 (9.3)
Hypertension	19 (6.2)	10 (13.3)
Cough	18 (5.9)	2 (2.7)
Urinary tract infection	15 (4.9)	3 (4.0)
Diabetic nephropathy	14 (4.6)	2 (2.7)
Diabetic neuropathy	12 (3.9)	2 (2.7)
Anemia	10 (3.3)	0
Hyperlipidemia	9 (2.9)	3 (4.0)
Alanine aminotransferase increased	3 (1.0)	4 (5.3)

The safety set included all patients who received at least one application of study treatment and has at least one post-baseline safety assessment. A patient with multiple incidences of an AE under one treatment was counted only once in the AE category. AEs with start date on or after the date of first administration of study treatment in the study eye were counted

AE adverse event, *IOP* intraocular pressure, *PRN* pro re nata

Table 5 Ocular (study eye; all patients) and non-ocular (≥ two patients in any arm) serious adverse events regardless of study drug relationship by preferred term (safety set)

Preferred term, *n* (%)	Ranibizumab 0.5 mg PRN (*n* = 307)	Laser (*n* = 75)
Ocular SAEs (total)	1 (0.3)	1 (1.3)
Cataract	1 (0.3)	0
Vitreous hemorrhage	0 (0.0)	1 (1.3)
Non-ocular SAEs (total)	49 (16.0)	11 (14.7)
Diabetes mellitus inadequate control	4 (1.3)	2 (2.7)
Diabetic neuropathy	3 (1.0)	1 (1.3)
Angina unstable	2 (0.7)	0
COPD	2 (0.7)	0
Diabetic vascular disorder	2 (0.7)	0
Hypertension	2 (0.7)	1 (1.3)
Hypoglycemia	2 (0.7)	0
Lung infection	2 (0.7)	0
Pneumonia	2 (0.7)	0
Diabetic foot	1 (0.3)	2 (2.7)
Death[a]	2 (0.7)	0
Sudden death	1 (0.3)	0
Pneumonia	1 (0.3)	0

The safety set included all patients who received at least one application of study treatment and has at least one post-baseline safety assessment

A patient with multiple occurrences of an SAE under one treatment was counted only once in the SAE category

SAEs with start date on or after the date of first administration of study treatment in the study eye were counted

COPD chronic obstructive pulmonary disease, *PRN* pro re nata, *SAE* serious adverse event

[a] Not related to the study drug

in LS means between both treatment arms was statistically significant ($p < 0.001$) and clinically meaningful. This improvement in BCVA was rapid during the first 3 months and was maintained throughout Month 12 in patients treated with ranibizumab 0.5 mg, while there was no meaningful improvement in BCVA in patients treated with laser. Anatomical outcomes further supported these functional improvements where the reduction in CSFT was higher in patients treated with ranibizumab than those treated with laser. More patients gained ≥ 10 and ≥ 15 letters in the ranibizumab arm than in the laser arm. With regard to the DR severity as assessed by the CRC, results demonstrated that more patients improved in the ranibizumab arm compared with the laser arm. This effect was more prominent in the group of patients with moderately severe NPDR or worse at baseline, where more than half of patients in the ranibizumab arm improved by 2 or more steps on the ETDRS-DRSS 10-point scale.

The findings of REFINE are consistent with the previous pivotal studies such as RESOLVE[16] and RESTORE[17]. The mean change in BCVA letter score from baseline at Month 12 among REFINE, RESOLVE[15], and RESTORE[16] studies was similar in the ranibizumab arm (7.8, 10.3, 6.8 letters, respectively) and the laser arm (2.5, − 1.4, 0.9 letters, respectively). A comparable proportion of patients gained ≥ 10 letters as well as ≥ 15 letters in the ranibizumab arm from baseline at Month 12 in REFINE, RESOLVE[16], and RESTORE[17] (gain of ≥ 10 letters 40.6%, 60.8%, 37.4%, respectively; and gain of ≥ 15 letters 18.5%, 32.4%, 22.6%, respectively). At Month 12, the mean number of ranibizumab injections was also similar among the REFINE, RESOLVE[16], and RESTORE[17] studies (7.9, 10.2, and 7.0, respectively).

Ranibizumab 0.5 mg was well-tolerated in the Chinese patients with visual impairment due to DME. Overall, the ocular and non-ocular AEs reported in the study eye were comparable between treatment arms, and no new AEs related to ranibizumab safety concerns were identified. The safety signals were consistent with the well-established safety profile of ranibizumab in previous DME studies [15, 16, 21].

Due to the nature of this study, there was no ethnical diversity and the study population was limited to mainland China. The REFINE study is the first to represent a large Chinese patient population with visual impairment due to DME. This study was adequately powered and therefore yielded highly significant results. The study was well-controlled and the central reading center ensured consistent interpretation of the anatomical outcomes.

In conclusion, given the clinical benefit achieved in the ranibizumab arm and the well-established safety profile of ranibizumab, the REFINE study results support the use of ranibizumab 0.5 mg PRN in Chinese patients with visual impairment due to DME.

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